ANDA 74-761

MAY 16 1997

Mylan Pharmaceuticals, Inc
Attention: Frank R. Sisto
P.O. Box 4310
781 Chestnut Ridge Road
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated September 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketorolac Tromethamine Tablets USP, 10 mg.

Reference is also made to your amendment dated March 4, 1997.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ketorolac Tromethamine Tablets USP, 10 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Toradol® Tablets, 10 mg, of Syntex Labs., Inc. Subsidary of Syntex Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

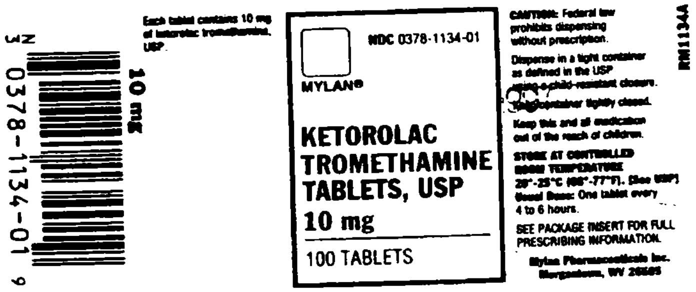
Sincerely yours,

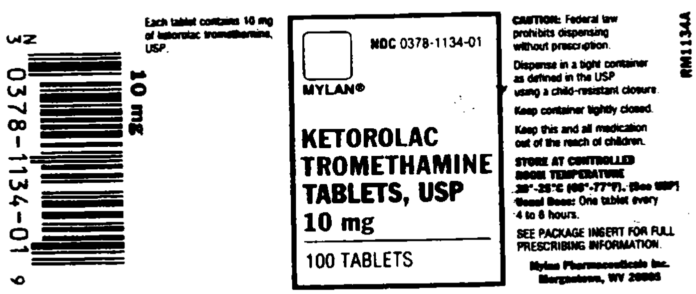
/S/ [redacted] 5-16-97

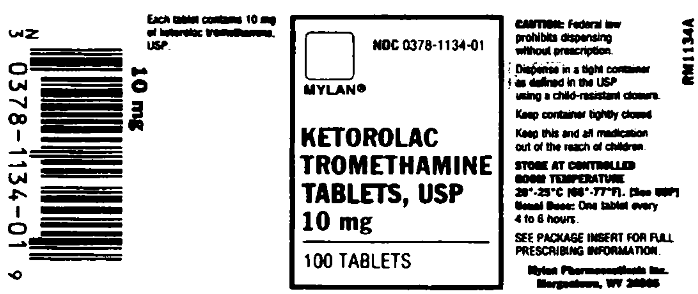
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

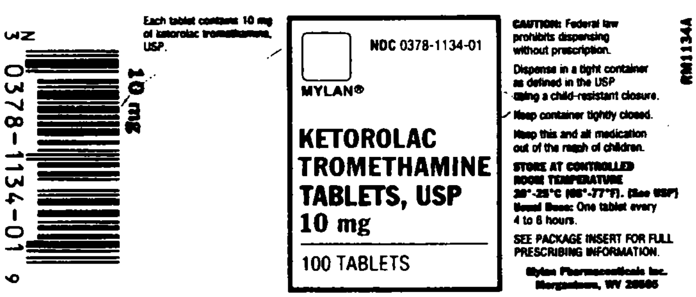
MYLAN PHARMACEUTICALS INC.

KETOROLAC TROMETHAMINE
TABLETS, USP
ANDA 74-761









MYLAN PHARMACEUTICALS INC.

KETOROLAC TROMETHAMINE
TABLETS, USP
ANDA 74-761

N 3 0378-1134-05 7

10 mg

Each tablet contains 10 mg of ketorolac tromethamine, USP.

NDC 0378-1134-05

MYLAN®

KETOROLAC TROMETHAMINE TABLETS, USP
10 mg

500 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

STORE AT CONTROLLED ROOM TEMPERATURE 20°-25°C (68°-77°F). [See USP]

Usual Dose: One tablet every 4 to 6 hours.

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1134B

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NDC 0378-1134-05

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Morgantown, WV 26505

RM1134B

KETOROLAC TROMETHAMINE TABLETS, USP
10 mg

MAY 16 1997

KTLC:R1

WARNING

Ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days) management of moderately severe, acute pain, that requires analgesia at the opioid level. It is NOT indicated for minor or chronic painful conditions. Ketorolac tromethamine is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately. Increasing the dose of ketorolac tromethamine beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

GASTROINTESTINAL EFFECTS

- **Ketorolac tromethamine can cause peptic ulcers, gastrointestinal bleeding, and/or perforation. Therefore, ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.**

RENAL EFFECTS

- **Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion (see WARNINGS).**

RISK OF BLEEDING

- **Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).**
- **Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intra-operatively when hemostasis is critical because of the increased risk of bleeding.**

HYPERSENSITIVITY

- **Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of ketorolac tromethamine-IV/IM (see CONTRAINDICATIONS and WARNINGS). Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).**

LABOR, DELIVERY, AND NURSING

- **The use of ketorolac tromethamine in labor and delivery is CONTRAINDICATED because it may adversely effect fetal circulation and the uterus.**
- **The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates.**

CONCOMITANT USE WITH NSAIDs

- **Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.**

DOSAGE AND ADMINISTRATION

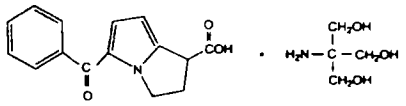
KETOROLAC TROMETHAMINE TABLETS

- **Ketorolac tromethamine tablets are indicated only as continuation therapy to ketorolac tromethamine-IV/IM, and the combined duration of use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 (five) days, because of the increased risk of serious adverse events.**
- **The recommended total daily dose of ketorolac tromethamine tablets (maximum 40 mg) is significantly lower than for ketorolac tromethamine-IV/IM (maximum 120 mg) (see DOSAGE and ADMINISTRATION and *Transition from ketorolac tromethamine-IV/IM to ketorolac tromethamine tablets*).**

SPECIAL POPULATIONS

- **Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs) of body weight (see DOSAGE and ADMINISTRATION), and for patients with moderately elevated serum creatinine (see WARNINGS).**

DESCRIPTION: Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol, and the structural formula is:



$C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$

Ketorolac tromethamine is a racemic mixture of (-)S and (+)R ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac tromethamine has a pKa of 3.5 and an *n*-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.41.

Each tablet for oral administration contains 10 mg ketorolac tromethamine. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, glyceryl triacetate, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY: Pharmacodynamics: Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). Ketorolac tromethamine inhibits synthesis of prostaglandins and may be considered a peripherally acting analgesic. The biological activity of ketorolac tromethamine is associated with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

Pain relief was statistically different after ketorolac tromethamine dosing from that of placebo at 1/2 hour (the first time point at which it was measured) following the largest recommended doses of ketorolac tromethamine, and by 1 hour following the smallest recommended doses. The peak analgesic effect occurred within 2 to 3 hours and was not statistically significantly different over the recommended dosage range of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine by either route was in the duration of analgesia.

Pharmacokinetics: Ketorolac tromethamine is a racemic mixture of (-)S- and (+)R-enantiomeric forms, with the S-form having analgesic activity.

Comparison of IV, IM, and Oral Pharmacokinetics: The pharmacokinetics of ketorolac tromethamine, following IV, IM, and oral doses of ketorolac tromethamine, are compared in Table 1. The extent of bioavailability following administration of the oral and IM forms of ketorolac tromethamine was equal to that following an IV bolus.

Linear Kinetics: Following administration of single oral, IM, or IV doses of ketorolac tromethamine, in the recommended dosage ranges, the clearance of the racemate does not change. This implies that the pharmacokinetics of ketorolac tromethamine in humans, following single or multiple IM, IV, or recommended oral doses of ketorolac tromethamine, are linear. At the higher recommended doses, there is a proportional increase in the concentrations of free and bound racemate.

Binding and Distribution: The ketorolac tromethamine racemate has been shown to be highly protein-bound (99%). Nevertheless, even plasma concentrations as high as 10 mcg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

The mean apparent volume (V_β) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single dose data.

Metabolism: Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

Clearance and Excretion: A single-dose study with 10 mg ketorolac tromethamine (n=9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer, and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans. The clearance of the racemate in normal subjects, elderly individuals, and in hepatically and renally impaired patients, is outlined in Table 2.

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ± 0.4) compared with 5 hours (SD ± 1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to be within the range of 5 to 6 hours.

Accumulation: Ketorolac tromethamine administered as an IV bolus, every 6 hours, for 5 days, to healthy subjects (n=13), showed no significant difference in C_{max} on Day 1 and Day 5. Trough levels averaged 0.29 mcg/mL (SD ± 0.13) on Day 1 and 0.55 mcg/mL (SD ± 0.23) on Day 6. Steady-state was approached after the fourth dose.

Accumulation of ketorolac tromethamine has not been studied in special populations (elderly patients, renal failure patients, or hepatic disease patients).

Effect of Food: Oral administration of ketorolac tromethamine after a high fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the extent of absorption.

Kinetics in Special Populations: Elderly Patients: Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5 to 7 hours in the elderly (65-78 years) compared with young healthy volunteers (24-35 years) (see Table 2). There was little difference in the C_{max} for the two groups (elderly, 2.52 mcg/mL ± 0.77; young, 2.99 mcg/mL ± 1.03) (see PRECAUTIONS—Use in the Elderly).

Renally Impaired Patients: Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r=0.5).

In patients with renal disease, the AUC_∞ of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC_∞ ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects (see WARNINGS—Renal Effects).

Hepatic Effects: There was no significant difference in estimates of half-life, AUC_∞, C_{max}, in 7 patients with liver disease compared to healthy volunteers (see PRECAUTIONS—Hepatic Effects).

TABLE 1

Table of Approximate Average Pharmacokinetic Parameters (Mean ±SD)
Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

Pharmacokinetic Parameters (units)	Oral†	Intramuscular*			Intravenous Bolus‡	
	10mg	15mg	30mg	60mg	15mg	30mg
Bioavailability (extent)		100%				
T_{max}[1] (min)	44 ± 34	33 ± 21**	44 ± 29	33 ± 21**	1.1 ± 0.7**	2.9 ± 1.8
C_{max}[2] (mcg/mL)(single dose)	0.87 ± 0.22	1.14 ± 0.32**	2.42 ± 0.68	4.55 ± 1.27**	2.47 ± 0.51**	4.65 ± 0.96
C_{max} (mcg/mL)(steady state q.i.d.)	1.05 ± 0.26**	1.56 ± 0.44**	3.11 ± 0.87**	N/A††	3.09 ± 1.17**	6.85 ± 2.61
C_{min}[3] (mcg/mL)(steady state q.i.d.)	0.29 ± 0.07**	0.47 ± 0.13**	0.93 ± 0.26**	N/A	0.61± 0.21**	1.04 ± 0.35
C_{ave}[4] (mcg/mL)(steady state q.i.d.)	0.58 ± 0.20**	0.94 ± 0.29**	1.88 ± 0.58**	N/A	1.09 ± 0.30**	2.17 ± 0.59
Vd[5] (L/kg)	0.175 ± 0.039				0.210 ± 0.044	

% Dose metabolized=<50 % Dose excreted in feces=6
% Dose excreted in urine=91 % Plasma protein binding=99

† Derived from PO pharmacokinetic studies in 77 normal fasted volunteers
* Derived from IM pharmacokinetic studies in 54 normal volunteers
‡ Derived from IV pharmacokinetic studies in 24 normal volunteers
†† Not Applicable because 60 mg is only recommended as a single-dose
** Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C_{max} and T_{max} data.
[1]Time-to-peak plasma concentration [4]Average plasma concentration
[2]Peak plasma concentration [5]Volume of Distribution
[3]Trough plasma concentration

TABLE 2

The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-life of Ketorolac Tromethamine (IM[a] and Oral[b])

Types of Subjects	Total Clearance (in L/h/kg)[3]		Terminal Half-Life (in hours)	
	IM Mean(range)	ORAL Mean(range)	IM Mean(range)	ORAL Mean(range)
Normal Subjects IM (n=54)mean age=32, range=18-60 Oral (n=77) mean age=32, range=20-60	0.023 (0.010-0.046)	0.025 (0.013-0.050)	5.3 (3.5-9.2)	5.3 (2.4-9.0)
Healthy Elderly Subjects IM (n=13), Oral (n=12) mean age =72, range =65-78	0.019 (0.013-0.034)	0.024 (0.018-0.034)	7.0 (4.7-8.6)	6.1 (4.3-7.6)
Patients with Hepatic Dysfunction IM and Oral (n=7) mean age=51, range=43-64	0.029 (0.013-0.066)	0.033 (0.019-0.051)	5.4 (2.2-6.9)	4.5 (1.8-7.6)
Patients with Renal Impairment IM (n=25); Oral (n=9) serum creatinine=1.9-5.0 mg/dL mean age (IM)=54, range 35-71 mean age (oral)=67, range=39-70	0.015 (0.005-0.043)	0.016 (0.007-0.052)	10.3 (5.9-19.2)	10.8 (3.4-18.9)
Renal Dialysis Patients IM and Oral (n=9), mean age=40, range=27-63	0.016 (0.003-0.036)	——	13.6 (8.8-30.1)	——

[a]Estimated from 30 mg single IM doses of ketorolac tromethamine
[b]Estimated from 10 mg single oral doses of ketorolac tromethamine
[3]Liters/hour/kilogram

IV Administration: In normal subjects (n=37), the total clearance of 30 mg IV administered ketorolac tromethamine was 0.030 (0.017-0.051) L/h/kg. The terminal half-life was 5.6 (4.0-7.9) hours.

Metabolism: Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

Clearance and Excretion: A single-dose study with 10 mg ketorolac tromethamine (n=9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer, and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans. The clearance of the racemate in normal subjects, elderly individuals, and in hepatically and renally impaired patients, is outlined in Table 2.

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Accumulation of ketorolac tromethamine has not been studied in special populations (elderly patients, renal failure patients, or hepatic disease patients).

Effect of Food: Oral administration of ketorolac tromethamine after a high fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the extent of absorption.

Kinetics in Special Populations: Elderly Patients: Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5 to 7 hours in the elderly (65-78 years) compared with young healthy volunteers (24-35 years) (see Table 2). There was little difference in the C_{max} for the two groups (elderly, 2.52 mcg/mL ± 0.77; young, 2.99 mcg/mL ± 1.03) (see PRECAUTIONS—Use in the Elderly).

Renally Impaired Patients: Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r=0.5).

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$C_{min_{ss}}$ (mcg/mL)(steady state q.i.d.)	1.05 ± 0.26**	1.56 ± 0.44**	3.11 ± 0.87**	NA[11]	3.09 ± 1.17**	6.85 ± 2.61
C_{min}[3] (mcg/mL)(steady state q.i.d.)	0.29 ± 0.07**	0.47 ± 0.13**	0.93 ± 0.26**	NA	0.61 ± 0.21**	1.04 ± 0.35
C_{ave}[4] (mcg/mL)(steady state q.i.d.)	0.59 ± 0.20**	0.94 ± 0.29**	1.86 ± 0.58**	NA	1.09 ± 0.30**	2.17 ± 0.59
Vd[5] (L/kg)	0.175 ± 0.039				0.210 ± 0.044	

Dose metabolized=<50 % Dose excreted in feces=6
Dose excreted in urine=91 % Plasma protein binding=99
Derived from PO pharmacokinetic studies in 77 normal fasted volunteers
Derived from IM pharmacokinetic studies in 54 normal volunteers
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Renal Dialysis Patients IM and Oral (n=9), mean age=40, range=27-63	0.016 (0.003-0.036)	—	13.6 (8.9-30.1)	—

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timated from 10 mg single oral doses of ketorolac tromethamine
ers/hour/kilogram
Administration: In normal subjects (n=37), the total clearance of 30 mg IV administered ketorolac tromethamine was 0.030 (0.017-0.051) L/h/kg. The terminal half-life was 5.6 (4.0-7.9) hours.

Clinical Studies: The analgesic efficacy of intramuscularly, intravenously and orally administered ketorolac tromethamine was investigated in two postoperative pain models: general surgery (orthopedic, gynecologic and abdominal) and oral surgery (removal of impacted third molars). The studies were double-blind, single- and multiple-dose, parallel trial designs, in patients with moderate to severe pain at baseline. Ketorolac tromethamine-IV/IM was compared as follows: IM to meperidine or morphine administered intramuscularly, and IV to morphine administered either directly IV or through a PCA (Patient-Controlled Analgesia) pump.

Short-Term Use (up to 5 days) Studies: In the comparisons of intramuscular administration during the first hour, the onset of analgesic action was similar for ketorolac tromethamine and the narcotics, but the duration of analgesia was longer with ketorolac tromethamine than with the opioid comparators meperidine or morphine.

In a multi-dose, postoperative (general surgery) double-blind trial of ketorolac tromethamine-IM 30 mg versus morphine 6 and 12 mg IM, each drug given on an "as needed" basis for up to 5 days, the overall analgesic effect of ketorolac tromethamine-IM 30 mg was between that of morphine 6 and 12 mg. The majority of patients treated with either ketorolac tromethamine or morphine were dosed for up to 3 days; a small percentage of patients received 5 days of dosing.

In clinical settings where perioperative morphine was allowed, ketorolac tromethamine-IV 30 mg, given once or twice as needed, provided analgesia comparable to morphine 4 mg IV once or twice as needed.

There was relatively limited experience with 5 consecutive days of ketorolac tromethamine-IV use in controlled clinical trials, as most patients were given the drug for 3 days or less. The adverse events seen with IV-administered ketorolac tromethamine were similar to those observed with IM-administered ketorolac tromethamine, as would be expected based on the similar pharmacokinetics and bioequivalence (AUC, clearance, plasma half-life) of IV and IM routes of ketorolac tromethamine administration.

Clinical Studies with Concomitant Use of Opioids: Clinical studies in postoperative pain management have demonstrated that ketorolac tromethamine-IV/IM, when used in combination with opioids, significantly reduced opioid consumption. This combination may be useful in the subpopulation of patients especially prone to opioid-related complications. Ketorolac tromethamine and narcotics should not be administered in the same syringe.

In a postoperative study, where all patients received morphine by a PCA device, patients treated with ketorolac tromethamine-IV as fixed intermittent boluses (e.g., 30 mg initial dose followed by 15 mg q.3h), required significantly less morphine (26%) than the placebo group. Analgesia was significantly superior, at various postdosing pain assessment times, in the patients receiving ketorolac tromethamine-IV plus PCA morphine as compared to patients receiving PCA-administered morphine alone.

Postmarketing Surveillance Study: A large postmarketing observational, non-randomized study, involving approximately 10,000 patients receiving ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal (G.I.) bleeding was dose-dependent (see Table 3A and 3B). This was particularly true in elderly patients who received an average daily dose greater than 60 mg/day of ketorolac tromethamine (Table 3A).

Table 3

Incidence of Clinically Serious G.I. Bleeding as Related to Age, Total Daily Dose, and History of G.I. Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine IV/IM

A. Patients without History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine IV/IM			
	≤ 60 mg	> 60 to 90 mg	> 90 to 120 mg	> 120 mg
< 65 years of age	0.4%	0.4%	0.9%	4.6%
≥ 65 years of age	1.2%	2.8%	2.2%	7.7%

B. Patients with History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine IV/IM			
	≤ 60 mg	> 60 to 90 mg	> 90 to 120 mg	> 120 mg
< 65 years of age	2.1%	4.6%	7.8%	15.4%
≥ 65 years of age	4.7%	3.7%	2.8%	25.0%

INDICATIONS AND USAGE: Ketorolac tromethamine is indicated for the short-term (≤5 days) management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with ketorolac tromethamine-IV/IM, and ketorolac tromethamine tablets are to be used only as continuation treatment, if necessary. Combined use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses (see WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

CONTRAINDICATIONS (see also Boxed WARNING): Ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment, or in patients at risk for renal failure due to volume depletion (see WARNINGS for correction of volume depletion).

Ketorolac tromethamine is CONTRAINDICATED in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage.

The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates.

Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intraoperatively when hemostasis is critical because of the increased risk of bleeding.

Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete homeostasis, and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).

Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risks of inducing serious NSAID related adverse events.

The concomitant use of ketorolac tromethamine and probenecid is CONTRAINDICATED.

WARNINGS (see also Boxed WARNING): The combined use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5-days. The most serious risks associated with ketorolac tromethamine are:

Gastrointestinal Ulcerations, Bleeding and Perforation: Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or G.I. bleeding. Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine. Studies to date with NSAIDs have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Postmarketing experience with parenterally administered ketorolac tromethamine suggests that there may be a greater risk of gastrointestinal ulcerations, bleeding and perforation in the elderly.

The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine. In a non-randomized, in-hospital postmarketing surveillance study, comparing parenteral ketorolac tromethamine to parenteral opioids, higher rates of clinically serious G.I. bleeding were seen in patients <65 years of age who received an average total daily dose of more than 90 mg of ketorolac tromethamine-IV/IM per day (see CLINICAL PHARMACOLOGY—Postmarketing Surveillance Study).

The same study showed that elderly (≥65 years of age), and debilitated patients are more susceptible to gastrointestinal complications. A history of peptic ulcer disease was revealed as another risk factor that increases the possibility of developing serious gastrointestinal complications during ketorolac tromethamine therapy (see Tables 3A and B).

Impaired Renal Function: ***Ketorolac tromethamine should be used with caution in patients with impaired renal function, or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis.*** Renal toxicity with ketorolac tromethamine has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of ketorolac tromethamine may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate acute renal failure. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of ketorolac tromethamine therapy is usually followed by recovery to the pretreatment state.

Renal Effects: Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (see CLINICAL PHARMACOLOGY). Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION) and such patients should be followed closely. With the use of ketorolac tromethamine, there have been reports of acute renal failure, nephritis, and nephrotic syndrome.

Because patients with underlying renal insufficiency are at increased risk of developing acute renal failure, the risks and benefits should be assessed prior to giving ketorolac tromethamine to these patients. **Ketorolac tromethamine is CONTRAINDICATED IN PATIENTS WITH SERUM CREATININE CONCENTRATIONS INDICATING ADVANCED RENAL IMPAIRMENT (see CONTRAINDICATIONS).**

Hypovolemia should be corrected before treatment with ketorolac tromethamine is initiated.

Fluid Retention and Edema: Fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with ketorolac tromethamine. Therefore, ketorolac tromethamine should be used only very cautiously in patients with cardiac decompensation, hypertension, or similar conditions.

Hemorrhage: Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients who have coagulation disorders should be undertaken very cautiously, and these patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and prophylactic low-dose heparin (2500-5000 units q12h), warfarin and dextrans have not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, physicians should carefully weigh the benefits against the risks, and use such concomitant therapy in these patients only extremely cautiously. In patients who receive anticoagulants for any reason, there is an increased risk of intramuscular hematoma formation from administered ketorolac tromethamine-IM (see PRECAUTIONS — Drug Interactions). Patients receiving therapy that affects hemostasis should be monitored closely.

In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the perioperative use of ketorolac tromethamine-IV/IM. Therefore, perioperative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical (see WARNINGS and PRECAUTIONS).

Anaphylactoid Reactions: Anaphylactoid reactions may occur in patients without a known previous exposure or hypersensitivity to aspirin, ketorolac tromethamine, or other NSAIDs, or in individuals with a history of angioedema, bronchospastic reactivity (e.g., asthma), and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

PRECAUTIONS: General: ***Hepatic Effects: Ketorolac tromethamine should be used with caution in patients with impaired hepatic function, or a history of liver disease.*** Treatment with ketorolac tromethamine may cause elevations of liver enzymes, and in patients with pre-existing liver dysfunction it may lead to the development of a more severe hepatic reaction. The administration of ketorolac tromethamine should be discontinued in patients in whom an abnormal liver test has occurred as a result of ketorolac tromethamine therapy.

Hematologic Effects: Ketorolac tromethamine inhibits platelet aggregation and may prolong bleeding time; therefore, it is contraindicated as a preoperative medication and caution should be used when hemostasis is critical. Unlike aspirin, the inhibition of platelet function by ketorolac tromethamine disappears within 24 to 48 hours after the drug is discontinued. Ketorolac tromethamine does not appear to affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). In controlled clinical studies, where ketorolac tromethamine was administered intramuscularly or intravenously postoperatively, the incidence of clinically significant postoperative bleeding was 0.4% for ketorolac tromethamine compared to 0.2% in the control groups receiving narcotic analgesics.

Information for Patients: Ketorolac tromethamine is a potent NSAID and may cause serious side effects such as gastrointestinal bleeding or kidney failure, which may result in hospitalization and even fatal outcome.

Physicians, when prescribing ketorolac tromethamine, should inform their patients of the potential risks of ketorolac tromethamine treatment (see Boxed WARNING, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections). *Advise patients not to give ketorolac tromethamine tablets to other family members and to discard any unused drug.* Remember that the total duration of ketorolac tromethamine therapy is not to exceed 5 (five) days.

Drug Interactions: Ketorolac is highly bound to human plasma protein (mean 99.2%).

The *in vitro* binding of ***warfarin*** to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs 99.3%) when ketorolac plasma concentrations reach 5 to 10 mcg/mL. Ketorolac does not alter ***digoxin*** protein binding. *In vitro* studies indicate that, at therapeutic concentrations of ***salicylate*** (300 mcg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential two-fold increase in unbound ketorolac plasma levels. Therapeutic concentrations of ***digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin,*** and ***tolbutamide*** did not alter ketorolac tromethamine protein binding.

In a study involving 12 volunteers, ketorolac tromethamine tablets were co-administered with a single-dose of 25 mg ***warfarin***, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine-IV/IM was given with two doses of 5000 U of ***heparin*** to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2 to 11.4 min) compared to a mean of 6.0 minutes (3.4 to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously and patients should be closely monitored (see WARNINGS and PRECAUTIONS).

Ketorolac tromethamine-IV/IM reduced the diuretic response to ***furosemide*** in normovolemic healthy subjects by approximately 20% (mean sodium and urinary output decreased 17%).

Concomitant administration of ketorolac tromethamine tablets and ***probenecid*** resulted in decreased clearance of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8 mcg/h/mL) and terminal half-life increased approximately 2-fold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

Inhibition of renal ***lithium*** clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis inhibiting drugs. The effect of ketorolac tromethamine on plasma lithium has not been studied, but cases of increased lithium plasma levels during ketorolac tromethamine therapy have been reported.

Concomitant administration of ***methotrexate*** and some NSAIDs has been reported to reduce the clearance of methotrexate, enhancing the toxicity of methotrexate. The effect of ketorolac tromethamine on methotrexate clearance has not been studied.

In postmarketing experience, there have been reports of a possible interaction between ketorolac tromethamine-IV/IM and ***non-depolarizing muscle relaxants*** that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

Concomitant use of ***ACE inhibitors*** may increase the risk of renal impairment, particularly in volume depleted patients.

Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and ***antiepileptic drugs*** (phenytoin sodium, carbamazepine).

Hallucinations have been reported when ketorolac tromethamine was used in patients taking ***psychoactive drugs*** (fluoxetine HCl, thiothixene, alprazolam).

There is no evidence, in animal or human studies, that ketorolac tromethamine induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: An 18-month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg q.i.d., based on area-under-the-plasma-concentration curve (AUC)), and a 24-month study in rats at 5 mg/kg/day (0.5 times the human AUC), showed no evidence of tumorigenicity.

Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 mcg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

Pregnancy: ***Pregnancy Category C:*** Reproduction studies have been performed during organogenesis, using daily oral doses of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1.0 times the human AUC) in rats. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (0.14 times the human AUC), administered after gestation day 17, caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies of ketorolac tromethamine in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage (see CONTRAINDICATIONS).

Lactation and Nursing: After a single administration of 10 mg of oral ketorolac tromethamine to humans, the maximum milk concentration observed was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (q.i.d.), the maximum milk concentration was 7.9 ng/mL and the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers is CONTRAINDICATED.

Pediatric Use: Safety and efficacy in pediatric patients (less than 16 years of age) have not been established. Therefore, use of ketorolac tromethamine in pediatric patients is not recommended.

Use in the Elderly (≥65 years of age): Because ketorolac tromethamine may be cleared more slowly by the elderly (see CLINICAL PHARMACOLOGY) who are also more sensitive to the adverse effects of NSAIDs (see WARNINGS — Renal Effects), extra caution and reduced dosages (see DOSAGE AND ADMINISTRATION) must be used when treating the elderly with ketorolac tromethamine. The incidences and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine.

ADVERSE REACTIONS: Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as G.I. ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions, and liver failure (see Boxed WARNING, WARNINGS, PRECAUTIONS, and DOSAGE and ADMINISTRATION). These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

The adverse reactions listed below were reported in clinical trials as probably related to ketorolac tromethamine.

Incidence Greater Than 1%: (Percentage of incidence in parentheses for those events reported in 3% or more patients):

Body as a Whole: edema (4%).

Cardiovascular: hypertension.

Dermatologic: pruritus, rash.

Gastrointestinal: nausea (12%), dyspepsia (12%), gastrointestinal pain (13%), diarrhea (7%), constipation, flatulence, gastrointestinal fullness, vomiting, stomatitis.

Hemic and Lymphatic: purpura.

Nervous System: headache (17%), drowsiness (6%), dizziness (7%), sweating.

Incidence 1% or Less:

Body as a Whole: weight gain, fever, infections, asthenia.

Cardiovascular: palpitation, pallor, syncope.

Dermatologic: urticaria.

Gastrointestinal: gastritis, rectal bleeding, eructation, anorexia, increased appetite.

Hemic and Lymphatic: epistaxis, anemia, eosinophilia.

Nervous System: tremors, abnormal dreams, hallucinations, euphoria, extrapyramidal symptoms, vertigo, paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesis, stupor.

Respiratory: dyspnea, pulmonary edema, rhinitis, cough.

Special Senses: abnormal taste, abnormal vision, blurred vision, tinnitus, hearing loss.

Urogenital: hematuria, proteinuria, oliguria, urinary retention, polyuria, increased urinary frequency.

The following adverse events were reported from postmarketing experience.

Body as a Whole: hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema (see Boxed WARNING, WARNINGS), myalgia.

Cardiovascular: hypotension and flushing.

Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculo-papular rash, urticaria.

Gastrointestinal: peptic ulceration, GI hemorrhage, GI perforation (see Boxed WARNING, WARNINGS), melena, acute pancreatitis.

Hemic and Lymphatic: postoperative wound hemorrhage, rarely requiring blood transfusion (see Boxed WARNING, WARNINGS and PRECAUTIONS), thrombocytopenia, leukopenia.

Hepatic: hepatitis, liver failure, cholestatic jaundice.

Nervous System: convulsions, psychosis, aseptic meningitis.

Respiratory: asthma, bronchospasm.

Urogenital: acute renal failure (see Boxed WARNING, WARNINGS), flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome.

OVERDOSAGE: In controlled overdosage, daily doses of 360 mg of ketorolac tromethamine-IV/IM given for five days (3 times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage.

Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION: THE COMBINED DURATION OF USE OF KETOROLAC TROMETHAMINE-IV/IM AND KETOROLAC TROMETHAMINE TABLETS IS NOT TO EXCEED FIVE (5) DAYS. THE USE OF KETOROLAC TROMETHAMINE TABLETS IS ONLY INDICATED AS CONTINUATION THERAPY TO KETOROLAC TROMETHAMINE-IV/IM.

Ketorolac tromethamine-IV/IM may be used as a single, or multiple dose, on a regular or "prn" schedule for the management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of ketorolac tromethamine (see WARNINGS - Renal Effects). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

Ketorolac Tromethamine Tablets are indicated ONLY as continuation therapy to ketorolac tromethamine-IV/IM for the management of moderately severe, acute pain that requires analgesia at the opioid level. See also PRECAUTIONS — Information for Patients.

Transition from Ketorolac Tromethamine-IV/IM to Ketorolac Tromethamine Tablets: The recommended dose for ketorolac tromethamine tablets is as follows:

Patients <65 years of age: Two (2) tablets as a first oral dose for patients who received **60 mg IM single dose, 30 mg IV single dose or 30 mg multiple dose** ketorolac tromethamine-IV/IM followed by one (1) tablet of ketorolac tromethamine orally every 4 to 6 hours, not to exceed 40 mg/24h of oral ketorolac tromethamine.

Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One (1) tablet as a first oral dose for patients

Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and *antiepileptic drugs* (phenytoin sodium, carbamazepine).

Hallucinations have been reported when ketorolac tromethamine was used in patients taking *psychoactive drugs* (fluoxetine HCl, thiothoxene, alprazolam).

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Lactation and Nursing: After a single administration of 10 mg of oral ketorolac tromethamine to humans, the maximum milk concentration observed was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (q.i.d.), the maximum milk concentration was 7.9 ng/mL and the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers is CONTRAINDICATED.

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Use in the Elderly (≥65 years of age): Because ketorolac tromethamine may be cleared more slowly by the elderly (see CLINICAL PHARMACOLOGY) who are also more sensitive to the adverse effects of NSAIDs (see WARNINGS — Renal Effects), extra caution and reduced dosages (see DOSAGE AND ADMINISTRATION) must be used when treating the elderly with ketorolac tromethamine. The incidences and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine.

ADVERSE REACTIONS: Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as G.I. ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions, and liver failure (see Boxed WARNING, WARNINGS, PRECAUTIONS, and DOSAGE and ADMINISTRATION). These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

The adverse reactions listed below were reported in clinical trials as probably related to ketorolac tromethamine.

Incidence Greater Than 1%: (Percentage of incidence in parentheses for those events reported in 3% or more patients):

Body as a Whole: edema (4%).

Cardiovascular: hypertension.

Dermatologic: pruritus, rash.

Gastrointestinal: nausea (12%), dyspepsia (12%), gastrointestinal pain (13%), diarrhea (7%), constipation, flatulence, gastrointestinal fullness, vomiting, stomatitis.

Hemic and Lymphatic: purpura.

Nervous System: headache (17%), drowsiness (6%), dizziness (7%), sweating.

Incidence 1% or Less:

Body as a Whole: weight gain, fever, infections, asthenia.

Cardiovascular: palpitation, pallor, syncope.

Dermatologic: urticaria.

Gastrointestinal: gastritis, rectal bleeding, eructation, anorexia, increased appetite.

Hemic and Lymphatic: epistaxis, anemia, eosinophilia.

Nervous System: tremors, abnormal dreams, hallucinations, euphoria, extrapyramidal symptoms, vertigo, paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesis, stupor.

Respiratory: dyspnea, pulmonary edema, rhinitis, cough.

Special Senses: abnormal taste, abnormal vision, blurred vision, tinnitus, hearing less.

Urogenital: hematuria, proteinuria, oliguria, urinary retention, polyuria, increased urinary frequency.

The following adverse events were reported from postmarketing experience.

Body as a Whole: hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema (see Boxed WARNING, WARNINGS), myalgia.

Cardiovascular: hypotension and flushing.

Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculo-papular rash, urticaria.

Gastrointestinal: peptic ulceration, GI hemorrhage, GI perforation (see Boxed WARNING, WARNINGS), melena, acute pancreatitis.

Hemic and Lymphatic: postoperative wound hemorrhage, rarely requiring blood transfusion (see Boxed WARNING, WARNINGS and PRECAUTIONS), thrombocytopenia, leukopenia.

Hepatic: hepatitis, liver failure, cholestatic jaundice.

Nervous System: convulsions, psychosis, aseptic meningitis.

Respiratory: asthma, bronchospasm.

Urogenital: acute renal failure (see Boxed WARNING, WARNINGS), flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome.

OVERDOSAGE: In controlled overdosage, daily doses of 360 mg of ketorolac tromethamine-IV/IM given for five days (3 times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage.

Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION: THE COMBINED DURATION OF USE OF KETOROLAC TROMETHAMINE-IV/IM AND KETOROLAC TROMETHAMINE TABLETS IS NOT TO EXCEED FIVE (5) DAYS. THE USE OF KETOROLAC TROMETHAMINE TABLETS IS ONLY INDICATED AS CONTINUATION THERAPY TO KETOROLAC TROMETHAMINE-IV/IM.

Ketorolac tromethamine-IV/IM may be used as a single, or multiple dose, on a regular or "prn" schedule for the management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of ketorolac tromethamine (see WARNINGS - Renal Effects). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

Ketorolac Tromethamine Tablets are indicated ONLY as continuation therapy to ketorolac tromethamine-IV/IM for the management of moderately severe, acute pain that requires analgesia at the opioid level. See also PRECAUTIONS — Information for Patients.

Transition from Ketorolac Tromethamine-IV/IM to Ketorolac Tromethamine Tablets: The recommended dose for ketorolac tromethamine tablets is as follows:

Patients <65 years of age: Two (2) tablets as a first oral dose for patients who received **60 mg IM single dose, 30 mg IV single dose or 30 mg multiple dose** ketorolac tromethamine-IV/IM followed by one (1) tablet of ketorolac tromethamine orally every 4 to 6 hours, not to exceed 40 mg/24h of oral ketorolac tromethamine.

Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lbs) of body weight: One (1) tablet as a first oral dose for patients who received **30 mg IM single dose, 15 mg IV single dose or 15 mg multiple dose** ketorolac tromethamine-IV/IM followed by one (1) tablet of ketorolac tromethamine orally every 4 to 6 hours, not to exceed 40 mg/24h of oral ketorolac tromethamine.

Shortening the recommended dosing intervals may result in increased frequency and severity of adverse reactions.

The maximum combined duration of use (parenteral and oral ketorolac tromethamine) is limited to 5 days.

HOW SUPPLIED: Ketorolac Tromethamine Tablets, USP are available containing 10 mg of ketorolac tromethamine. The tablets are film-coated, white, unscored round tablets marked with M over 134 on one side and blank on the other side. They are available as follows:

NDC 0378-1134-01
bottles of 100 tablets
NDC 0378-1134-05
bottles of 500 tablets

STORE AT CONTROLLED ROOM TEMPERATURE 20°-25°C (68°-77°F). [See USP]

Dispense in a tight container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED APRIL 1996
KTLC:R1

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 74-761

3. NAME AND ADDRESS OF APPLICANT **Mylan Pharmaceuticals, Inc**
Attention: Frank R. Sisto
781 Chestnut Ridge Road, Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION Toradol® Tablets from Syntex
Patent 4089969 expires May 16, 1997

5. SUPPLEMENTS N/A 6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME **Ketorolac Tromethamine, USP**

8. SUPPLEMENTS PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
03-04-97 Minor Amendment - this review
09-16-96 Major Amendment
09-29-95 Original Submission

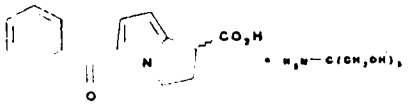
10. PHARMACOLOGICAL CATEGORY NSAID,short term management of pain

11. Rx

12. RELATED IND/NDA/DMF(s) (b)(4)CC [redacted]

13. DOSAGE FORM **tablet, oral,** white film coated, 5/16" round biconvex beveled edge tablet with M over 134 engraved on one side and plain on the reverse

14. POTENCY **10 mg**



15. CHEMICAL NAME AND STRUCTURE
$C_{15}H_{13}NO_3.C_4H_{11}NO_3$; M.W. = 376.41;
CAS [74103-07-4]
(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

16. RECORDS AND REPORTS N/A

17. COMMENTS *The Quality Control Review was done on this application. The file should be updated because the firm has modified some specifications since the review was done.*

18. CONCLUSIONS AND RECOMMENDATIONS **APPROVAL**

19. REVIEWER: Melissa Maust DATE COMPLETED: March 27, 1997
Updated: May 14, 1997

cc: ANDA 74-761
Division File
Endorsements: /S/ [redacted] 5/15/97
HFD-623/M.Maust
HFD-623/V. Saye
Y:\NEW\FIRMSAM\MYLAN\LTRS&REV\74761R3.TAP
F/T by

ANDA **74-761** APPROVAL SUMMARY

DRUG PRODUCT: **Ketorolac Tablets, USP**

FIRM: **Mylan Pharmaceuticals, Inc.**

DOSAGE FORM: **tablets** *STRENGTH*: **10 mg**

CGMP STATEMENT/EIR UPDATE STATUS: ACCEPTABLE, 01-21-97

BIO STUDY: APPROVE, letter sent 02-28-96

VALIDATION - DS and DP are compendial

STABILITY - 24 months room temperature and 3 months acclerated stability data for each strength are provided. The container/closure systems used for the stability study are equivalent to the systems proposed for commercial use. The stability data provided are within specifications as listed. Thus, a 24 month expiration date is justified.

Tests and specifications for drug product on stability include an appearance, dissolution (NLT (b)(4)CC Q) in 45 mins), related compounds (b)(4)CC

LABELING: APPROVE 10-24-96

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - The biobatches are the test batches. DS supplier is (b)(4)CC is adequate as of 03-24-97.

Strength	Test Batch Size	Production Batch Size
10 mg	(b)(4)CC	

SIZE OF STABILITY BATCHES - Stability batches are the biobatches.

PROPOSED PRODUCTION BATCHES - See chart above. The proposed production manufacturing process is the same (except for size of equipment and quantity of raw materials) as that used for the stability batches.

CHEMIST: /S/ DATE: 5-14-97
SUPERVISOR: DATE:

ANDA 74-761

FEB 28 1996

Mylan Pharmaceuticals, Inc.
Attention: Patrick K. Noonan, Ph.D.
781 Chestnut Ridge Road
Morgantown WV 26505-2730

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ketorolac Tromethamine Tablets USP, 10 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 600 mL of deionized water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

   Not less tha(b)(4)C(the labeled amount of the drug in the tablet is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/ [redacted]

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 2 3 1996

Ketorolac Tromethamine
10 mg Tablets
ANDA # 74-761
Reviewer: Man M. Kochhar

Mylan Pharmaceuticals
Morgantown, WV
Submission Date:
September 29, 1995

Review of Bioequivalence Study and Dissolution
(Fasting and Non-fasting)

OBJECTIVE:

The objective of this study was to determine the bioequivalence of the 10 mg generic ketorolac tromethamine tablet with the marketed 10 mg Toradol (Syntex) tablet in healthy subjects under fasting and non-fasting conditions. The effects of the food on the pharmacokinetics of ketorolac were also evaluated.

INTRODUCTION:

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs. It is a racemic mixture of [-]S and [+]R ketorolac tromethamine. It is soluble in water.

Ketorolac tromethamine is a nonsteroidal antiinflammatory drug. It acts peripherally through the inhibition of prostaglandin synthesis. The pharmacokinetics of ketorolac in humans, following single or multiple doses, are linear. Steady state plasma levels are achieved after dosing every 6 hours for approximately 24 hours. Oral ketorolac is completely absorbed following single dose administration of 10 mg ketorolac tromethamine. The mean peak concentration in plasma is 0.7 to 1.1 mcg/mL, occurring an average of 44 minutes after dosing under fasting conditions. The plasma half-life is 2.4 to 9 hours in young adults. A standardized meal decreased the peak concentration and delayed the time to peak concentration, but did not affect the extent of absorption.

IN-VIVO STUDY:

The objective of this study was to compare the bioavailability of Mylan and Syntex (Toradol) 10 mg tablets under fasting and non-fasting conditions.

The fasting bioequivalence study was conducted by Mylan Pharmaceuticals, Morgantown, WV, under the supervision of Thomas S. Clark, M.D., and Dorian Williams, M.D..

The non-fasting bioequivalence study was conducted by Novum, Inc.

(b)(4)CC

STUDY DESIGN:

Study #1. The study was designed as a randomized, two-way crossover single dose [illegible] 10 mg tablet [illegible] study in 36 healthy volunteers under fasting conditions (Protocol No. KETL-9512).

Study #2. The study was designed as a randomized, three-way crossover, single dose (10 mg tablet) study in 18 healthy volunteers under fasting and non-fasting conditions (Protocol No. 9500105).

Subjects:

Study #1 employed thirty six (36) (fasting condition) and study # 2 employed 18 (non-fasting condition), healthy male volunteers between 21 and 40 years of age and within ±10% of the ideal body weight for their height and body frame (Metropolitan Insurance Company Bulletin, 1983). Volunteers without history of asthma, nasal polyps, or serious cardiovascular, hepatic, renal, hematopoietic, peptic ulcer or gastrointestinal disease, alcohol or drug abuse were employed.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis, etc.). The volunteers were not allowed to take any prescription medications and/or OTC preparations for at least two weeks prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing and until completion of the study.

The subjects were housed in the live-in facility from 10 hours before until 24 hours after the drug administration.

Methods

The products and dosages employed in study # 1 were as follows:

FASTING

Treatment A. Test: One 10 mg tablet ketorolac tromethamine (test drug, Mylan), lot # 2A006L with 240 mL of water.
Batch Size: (b)(4)CC Manufactured: November '94
Potency: 98.5% Content Uniformity: 98.4%

Treatment B. Reference: One 10 mg tablet of Toradol (Syntex), lot #03219 with 240 mL of water. Expiry date: 6/96
Potency: 98.4% Content Uniformity: 99.4%

STUDY # 2

NON-FASTING

The product employed in this study were:

Treatment C. Test: One 10 mg tablet ketorolac tromethamine (test drug, Mylan) lot # 2A006L with 240 mL of water (Fasting).

Treatment D. Test: One 10 mg tablet ketorolac tromethamine (test drug, Mylan), lot # 2A006L with 240 mL of water (Non-fasting).

Treatment E. Reference: One 10 mg tablet of Toradol (Syntex), lot # 03219 with 240 mL of water (Non-Fasting).

In study # 1 subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 2 hour of drug administration.

In study # 2 (non-fasting) subjects fasted overnight until 20 minutes prior to their scheduled dosing times, when they were given a standard breakfast.

Ten (10) mL of venous blood were drawn in Vacutainers with heparin at 0, 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 7, 10, 14, 18, 24 and 48 hours. The serum was separated and promptly frozen for analysis.

WASHOUT PERIOD: 7 DAYS

ANALYTICAL METHODOLOGY:

(b)(4)CC

[redacted]

(b)(4)CC

[redacted]

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, and sequence) were carried out to compare plasma levels at

each sampling time, AUC (0-t), AUC (inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test) were calculated for ketorolac pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Study # 1

Treatment A and B

Of the 36 subjects enrolled in the study 34 subjects completed the crossover. One subject (#25) did not report for Phase II dosing and one subject (#27) was in violation of the protocol. The plasma samples from 34 subjects were assayed for ketorolac as per protocol. The results of the study comparing the bioavailability of ketorolac tromethamine tablet are given in Tables 1, and 2. The mean plasma ketorolac concentrations are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Ketorolac (N= 34)

Time (hours)	Mylan's Lot # 2A006L ng/mL (Std err)	Syntex's Lot # 03219 ng/mL (Std.err)	T/R
0.00	0.0	0.0	
0.17	294.20 (46)	181.42 (44)	1.62
0.33	678.35 (38)	551.39 (46)	1.23
0.5	715.31 (30)	676.77 (35)	1.05
0.75	627.49 (25)	640.11 (28)	0.98
1.0	553.70 (19)	577.59 (25)	0.96
1.25	490.89 (16)	523.04 (21)	0.94
1.5	444.81 (15)	470.96 (19)	0.94
2.0	373.22 (15)	391.69 (17)	0.95
3.0	276.82 (13)	288.24 (13)	0.96
4.0	215.25 (13)	219.30 (13)	0.98
5.0	170.18 (12)	176.20 (11)	0.96
6.0	130.53 (9)	136.90 (8)	0.95
7.0	104.99 (7)	111.34 (7)	0.94
8.0	82.44 (6)	85.62 (6)	0.96
10.0	52.13 (5)	53.50 (4)	0.97
12.0	39.95 (4)	41.44 (3)	0.96
16.0	19.16 (2)	19.37 (2)	0.99
24.0	6.14 (1)	5.72 (1)	1.07
48.0	0.0 (--)	0.00 (--)	0.00

TABLE 2

A Summary of Pharmacokinetic Parameters for 34 Subjects (Std. Dev.)

Parameters	Mylan's Mean (Std. Dev)	Syntex's Mean (Std.Dev.)	T/R	90% Confidence Interval
AUC_{0-48} ng.hr/mL	2533 (694)	2566 (674)	0.99	93; 104
AUC_{inf} ng.hr/mL	2636 (719)	2673 (694)	0.99	93; 104
C_{max} ng/mL	786 (135)	776 (139)	1.01	96; 107
T_{max} hours	0.52 (.34)	0.61 (.34)	0.85	
K_{el} 1/hr	0.1688 (.08)	0.1649 (.06)	1.02	
$t_{1/2}$ hours	4.86 (2)	4.73 (2)	1.03	
Ln AUC_{0-48} ng.hr/mL	7.80 (.28)	7.82 (.26)	0.99	93; 104
Ln AUC_{inf} ng.hr/mL	7.84 (.28)	7.86 (.26)	0.99	93; 104
Ln C_{max} ng/mL	6.65 (.18)	6.64 (.18)	1.00	96; 107

The ratios of arithmetic means (with 90% confidence intervals) for AUC_{0-48} and AUC_{inf} and C_{max} were 0.99 ([redacted], 0.99 [redacted] and 1.01 [redacted] respectively. The K_{el} and $t_{1/2}$ values differ by 2.37% and 2.75% respectively. The Tmax was 5.17 hours for the test product and 4.97 hours for the reference product. The firm did calculate Ln AUC and Ln Cmax for ketorolac and the 90% confidence intervals for log-transformed parameters were 93 to 104 for Ln AUCo-t, 93 to 104 for Ln AUCinf and 96 to 107 for Ln Cmax.

The ketorolac concentration/time profiles of the two products were same with less than 20% difference between the products being observed at each of the timed collection points.

Adverse Effects:

There were no serious adverse effects which required dropping any

subject from the study or required therapeutic medical intervention.

On the basis of fasting in vivo bioavailability data it is determined that Mylan's ketorolac tromethamine, 10 mg tablets and Syntex's Toradol tablets, 10 mg are bioequivalent.

Study # 2

The products employed in this study were:

Treatment C: Test: One 10 mg tablet ketorolac (test drug, Mylan), lot # 2A006L with 240 mL of water. (Fasting)
Batch Size: (b)(4)CC Manufactured: 11/ 1994

Treatment D: Test: One 10 mg tablet ketorolac (test drug, Mylan), lot # 2A006L with 240 mL of water (Non-Fasting Condition).

Treatment E: Reference: One 10 mg tablet of Toradol (Syntex) lot # 03219 240 mL of water (Non-Fasting condition). Expiry Date: 6/96

In Treatment C the subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 1 hour of drug administration.

In Treatment D and E, subjects fasted overnight until 20 minutes prior to their scheduled dosing times, when they were given a standard breakfast.

Ten (10) mL of venous blood were drawn in Vacutainers with heparin as anticoagulant at: 0, 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.50, 2, 2.5, 3, 5, 7, 10, 14, 18 and 24 hours post-drug.

WASHOUT PERIOD: 7 days

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Study # 2

Of the 18 subjects, 15 subjects successfully completed three phases of the study. Subject # 2, 5 and 13 did not show up for phase 2 for personal reasons. The plasma samples from first 15 subjects were assayed as per protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of ketorolac tablets are given in Tables 3 and 4. The mean plasma ketorolac concentrations are given in Figure 2.

TABLE 3

Mean Serum Concentration of Ketorolac (N=15)

Time hours	Mylan's Ketorolac (10 mg Tablet) ng/mL (Std.err.)		Syntex's Toradol (10 mg Tablet) ng/mL (Std. err.)		T/R (D/E)
	Fasting (Treat.C)	Non-fasting (Treat.D)	Non-fasting (Treat.E)		
0	0 (000)	0	0.00	(---)	0.00
0.17	446.54 (87)	128.93 (36)	88.16	(42)	0.00
0.25	690.94 (88)	248.37 (59)	151.22	(47)	1.64
0.33	858.77 (74)	325.30 (64)	237.45	(55)	1.37
0.50	895.33 (54)	408.32 (58)	342.55	(65)	1.19
0.75	786.90 (45)	450.14 (45)	412.89	(61)	1.09
1.00	685.65 (30)	466.06 (39)	429.29	(49)	1.08
1.25	606.42 (28)	449.87 (34)	434.36	(42)	1.03
1.50	551.98 (28)	433.33 (30)	419.25	(35)	1.03
2.00	478.43 (26)	392.44 (26)	389.05	(23)	1.00
2.50	413.18 (22)	342.10 (19)	369.30	(17)	0.93
3.00	358.91 (20)	307.45 (18)	355.90	(20)	0.86
5.00	234.99 (17)	248.63 (26)	267.12	(25)	0.93
7.00	146.31 (12)	154.41 (16)	166.87	(17)	0.92
10.00	84.65 (8)	85.92 (10)	86.64	(10)	0.99
14.00	47.73 (5)	44.58 (6)	48.95	(7)	0.91
18.00	29.12 (3)	28.08 (4)	29.93	(4)	0.94
24,00	16.01 (3)	15.86 (3)	15.88	(3)	1.00

TABLE 4

A SUMMARY OF PHARMACOKINETIC PARAMETERS FOR 15 SUBJECTS
Non-Fasting

Parameters	Mylan's Ketorolac 10 mg Tablet Mean (Std Dev) Fasting Treat. C	Non-Fasting Treat. D	Syntex's Toradol 10 mg Tablet Mean (Std Dev) Non-Fasting Treat. E	T/T (C/D)	T/R (D/E)
AUC_{0-t} ng.hr/mL	2536.0 (859)	2960.5 (724)	3060.9 (757)	0.86	0.97
AUC_{inf} ng.hr/mL	3743.2 (975)	3161.7 (831)	3243.1 (820)	1.18	0.97
C_{max} ng/mL	876.3 (183)	576.2 (144)	555.0 (143)	1.52	1.04
T_{max} hours	0.46 (.24)	1.35 (1.2)	1.56 (1.24)	0.34	0.87

$t_{½}$ hours	6.77 (2.3)	7.18 (2.3)	6.56 (1.29)	0.94	1.09
K_{el} 1/hr	0.1145 (.04)	0.1057 (.03)	0.1101 (.24)	1.08	0.96
Ln AUC_{0-t} ng.hr/mL	8.14 (.26)	7.96 (.25)	7.99 (.26)	1.02	0.99
Ln AUC_{inf} ng.hr/mL	8.19 (.27)	8.02 (.27)	8.05 (.27)	1.02	1.00
Ln C_{max} ng/mL	6.87 (.19)	6.32 (.27)	6.29 (.26)	1.08	**1.00**

The ketorolac AUCo-t and AUCinf produced by Mylan's formulation are 3.3% lower and 2.51% lower respectively than the respective values for the reference drug. The Cmax is 3.82% higher than the reference. The Tmax is 13.5% lower than the corresponding reference value. The Kel and t½ values differ by 4% and 9%.

The analysis of the plasma ketorolac data showed no significant differences in ketorolac concentrations at any time point.

Fasting-Nonfasting Comparison (Treatment C vs D) Mylan

The ratios of means for untransformed parameters were 0.86 and 1.18 for AUCo-t and AUCinf respectively and for Cmax the ratio was 1.52. The mean Tmax was 0.46 hours under fasting conditions and 1.35 hours under non-fasting conditions.

Nonfasting Comparison (Treatment D vs E) Mylan vs Syntex

The ratios of means (D/E) for the untransformed parameters, the AUCo-t, AUCinf and Cmax were 0.97, 0.97 and 1.04 respectively. Mean Tmax values were 1.35 hours and 1.56 hours for Mylan (Treatment D) and Syntex (Treatment E) products, respectively. The ratios for Kel and t1/2 were 0.96 and 1.09 respectively. The ratios for log-transformed parameters AUCo-t, AUCinf and Cmax were 0.99, 1.00, and 1.00 respectively.

There were no adverse events reported during the study.

Based on the Mylan (D) to Toradol (E) comparison, the relative ratios for AUCo-t, AUCinf, and Cmax were evaluated to be within the 80 - 120 range.

Based on the relative ratios for the AUCs and Cmax, it can be concluded that a single dose of one ketorolac 10 mg tablet (Mylan) and a single dose of one Toradol 10 mg tablet (Syntex) are bioequivalent when taken under non-fasting conditions.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 600 mL of distilled water at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The results for 10 mg tablets are presented in Table 5.

COMMENTS:

FASTING

Study # 1

1. Of the 36 subjects enrolled in the study, 34 completed the crossover. The plasma samples from the 34 subjects were assayed for ketorolac as per protocol. The plasma concentration of the test 10 mg ketorolac tablet was compared to the reference Toradol 10 mg tablet. The keorolac T/R ratios for AUCo-t, AUCinf and Cmax for 10 mg tablets were well within the range of 0.8 to 1.2.

2. Analysis of variance indicated no statistically significant treatment differences for AUC and Cmax for ketorolac 10 mg tablets. The 90% confidence intervals are within 80% to 125% for all the log transformed pharmacokinetic parameters.

3. The assay validation studies conducted by the sponsor are acceptable to the Division of Bioequivalence.

4. No serious adverse reactions were observed by any subject.

5. The in vitro dissolution testing conducted for 10 mg tablets of the test and reference shows not less than (b)(4)(c) of the drug dissolved in 45 minutes.

6. The in vivo fasting bioequivalence study and in vitro dissolution testing for 10 mg tablet is acceptable.

NON-FASTING:

Study # 2

1. The ratios for AUCo-t, AUCinf and Cmax of the test and reference formulation were 0.97, 0.97 and 1.04 respectively. The ratios for these parameters were well within the limits set by the Division of Bioequivalence. Plasma ketorolac data showed no statistically significant differences in products for any of the pharmacokinetic parameters.

2. The Mylan and Syntex Toradol 10 mg tablets appear to show comparable bioavailability under non-fasting conditions. Administration of ketorolac with food, decreased the extent of absorption (AUCinf), decreased the Cmax and delayed the rate of absorption (prolonged Tmax).

3. No serious clinical events were recorded during this period.

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting and non-fasting bioequivalence studies conducted by Mylan Pharmaceuticals on its Ketorolac Tromethamine tablets, 10 mg lot # 2A006L, comparing it to Toradol tablets, 10 mg, lot # 03219, manufactured by Syntex has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting and non-fasting conditions the Mylan's Ketorolac Tromethamine 10 mg tablets are bioequivalent to the reference product, Toradol 10 mg tablets manufactured by Syntex.

2. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 mL of deionized water at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

> Not less than (b)(4) of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

3. The firm should be informed of the recommendations.

/S/

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE /S/ 2/20/96
FT INITIALLED RMHATRE

Concur: /S/ Date: 2/23/96

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MMKochhar/mmk/2-7-96; 74-761 BIO

cc: ANDA # 74-761 original, HFD-630, HFD-600 (Hare), HFD-344 (CVisvanathan), HFD-658 (Mhatre, Kochhar), Drug File.

(Please select Typeover for Input.)

Table 3 . In Vitro Dissolution Testing

Drug (Generic Name): Ketorolac Tromethamine
Dose Strength: 10 mg
ANDA No.: 74-761
Firm: Mylan
Submission Date: September 29, 1995
File Name:

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Volume: 600 mL deionized water
Specifications: NLT (b)(4)CC in 45 minutes
Reference Drug: Toradol

Assay Methodology (b)(4)CC

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 2A006L Strength 10 MG			Reference Product Lot # 03219 Strength 10 MG		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96	(b)(4)CC	2.2	87	(b)(4)CC	8.0
30	100		1.8	93		6.2
45	101		1.4	96		5.5

TABLE 6

FORMULATION

INGREDIENTS	**10 mg Tablets**
Ketorolac Tromethamine	10.00 mg
Lactose (b)(4)TS NF	(b)(4)TS
Microcrystalline Cellulose NF	
Magnesium Stearate NF	
Colloidal Silicon Dioxide	
Croscarmellose Sodium	
Total	200.00 mg
Film Coating:	
(b)(4)TS	
Purified Water, USP	---

Figure 1

KETOROLAC (KETL 9512)

Mean Ketorolac Plasma Concentrations

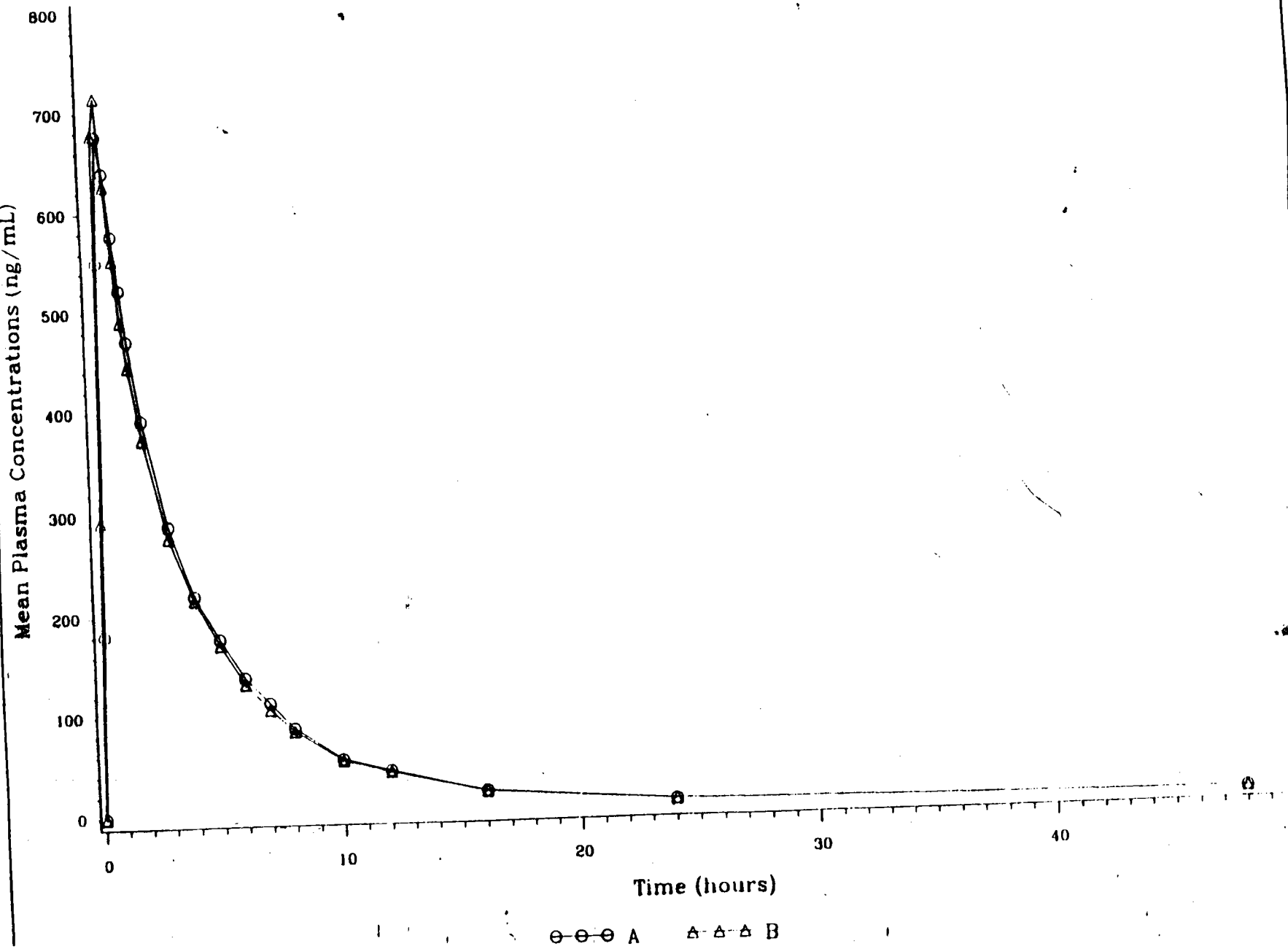

Figure 2

KETOROLAC (KETL-9513)

Mean Ketorolac Plasma Concentrations